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09/061,417	04/16/1998	ERIC N. OLSON	UTSD:548	1649

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STEVEN L. HIGHLANDER  
FULBRIGHT AND JAWORSKI  
P O BOX 4433  
600 CONGRESS AVE, SUITE 78701  
AUSTIN,, TX 78701

EXAMINER

DAVIS, MINH TAM B

ART UNIT

PAPER NUMBER

1642

DATE MAILED: 07/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application N .

09/061,417

Applicant(s)

OLSON ET AL.

Examiner

MINH-TAM DAVIS

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 08 May 2003.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,4 and 9 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,4 and 9 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)                      4) ☒ Interview Summary (PTO-413) Paper No(s). 25
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)                      5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_                      6) ☐ Other:

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### **DETAILED ACTION**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The finality of the previous Office action has been withdrawn, and the prosecution of this application is reopened to reinstate a previous rejection.

It is noted that applicant has paid for a Notice of Appeal. Applicant can either request a refund or place the funds on credit for future appeals.

Accordingly, claims 1, 4, 9 are examined in the instant application.

### **REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION**

Rejection under 35 USC, 112 first paragraph, written description of claims 1, 4, 9 in paper No:18, on 04/24/02 is reinstated.

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims 1, 4, 9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

*Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought,

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he or she was in possession of *the invention*. The invention is, for purposes of the written description inquiry, *whatever is now claimed*. (See page 1117). The specification does not clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. (See *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Claims 1, 4, 9 are drawn to a method for treating hypertrophy in a cardiomyocyte cell, comprising contacting NF-AT3 with an agent that binds to and inactivates NF-AT3, wherein said agent is a "small molecule inhibitor."

The specification contemplates the use of a single chain antibody or an antisense molecule that could inhibit the binding of NF-AT3 to calcineurin (p.4, last paragraph, and p.28-29). The specification also contemplates the use of a mimetic of beta-turns within GATA4, that binds to NF-AT3 in a manner analogous to the transcriptional factor GATA4, and specifically inhibits NF-AT3 binding to GATA4 (p.29). The structure of the mimetics of beta-turns within GATA4 and of antisense molecules however is not disclosed

Although drawn specifically to the DNA art, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly relevant to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved

by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA... requires a precise definition, such as by structure, formula, chemical name, or physical properties", not a mere wish or plan for obtaining the claimed chemical invention.

The claims, as written, however, encompass a method for treating hypertrophy of a cardiomyocyte cell, comprising contacting NF-AT3 with any small inhibitor molecules, such as mimetics having any structure or composition, the structure of which is not disclosed and is not necessarily similar to scFv of an antibody or an oligonucleotide such as an antisense molecule.

The instant disclosure of a single species of scFv of an antibody, does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera having diverse structure.

The instant specification fails to provide sufficient descriptive information, such as definitive structural features of the claimed genus of small molecule inhibitors. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Furthermore, although molecular modeling is known in the art, the structure of the claimed small molecule inhibitors is not known. The prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the small molecules encompassed and no identifying characteristic

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or property of the instant small molecules is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, and further because the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus, the disclosure of a single chain of an antibody is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed. Thus, only a method for treating hypertrophy in a cardiomyocyte cell, comprising exposing to said cell sFv of an antibody that inhibits the binding of NF-AT3 to calcineurin, but not the full breadth of the claims meet the written description provisions of 35 USC 112, first paragraph.

#### **ANSWERS TO APPLICANT'S ARGUMENTS AGAINST REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION**

Applicant submits a Declaration by Dr. Rick Gorczynski in paper No:19.

Applicant argues in paper No:19 that the specification does not rely on function alone, specific examples and specific molecules are given so that one of skill in the art would be able to visualize or recognize the subject matter.

Applicant argues that knowledge of the actual binding site is not a requirement for one of skill in the art to appreciate that the inventors had possession of the claimed invention. Applicant asserts that as discussed in the Declaration by Dr. Rick Gorczynski, one would not doubt that GATA4 does indeed bind to NF-AT3, nor would they challenge the notion that interference with that interaction will have inhibitory effects on NF-AT3 ability to activate gene transcription of hypertrophic genes.

Applicant asserts that unlike the *Lilly* case, where the DNA molecules at issue had not yet been discovered, a number of the NF-AT3 targeting molecules disclosed by applicant are already known. Applicant asserts that the specification refers to GATA4 mimetics, antioxidant dithiocarbamates or DTC's which are small molecules that are inhibitors of NF-AT3, antisense molecules, antibody, competitive inhibitors of NF-AT3, which are known in the art.

Applicant argues that the description requirement does not demand exhaustive listing of molecules and detailed description of binding sites and binding regions.

The submission of the Declaration by Dr. Rick Gorczynski is acknowledged.

Applicant's arguments set forth in paper No.19 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that contrary to Applicant arguments, the structure of the claimed GATA4 mimetics, antisense molecules, and competitive inhibitors of NF-AT3 is not disclosed in the specification, nor is it ~~not~~ known in the art and does not seem to have any common structural attribute. Further, although DTC's is known in the art, they are

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not disclosed in the specification, and are not peptides and do not seem to have the same common structure as the contemplated mimetics of GATA4.

Thus there is no common structural attributes among the claimed small inhibitors, including the claimed GATA4 mimetics, antisense molecules, antibody, and competitive inhibitors of NF-AT3.

The instant specification thus fails to provide sufficient descriptive information, such as definitive structural features of the claimed genus of small molecule inhibitors. There is no description of the conserved regions or common structural attributes which are critical to the structure and function of the genus claimed. In the absence of the above descriptive information, and in view of the teaching of the court which held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus, one would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed. Thus, only a method for treating hypertrophy in a cardiomyocyte cell, comprising exposing to said cell sFv of an antibody that inhibits the binding of NF-AT3 to calcineurin, but not the full breadth of the claims meet the written description provisions of 35 USC 112, first paragraph.

#### **REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE, NEW REJECTION**

Claims 1, 4, 9 are rejected under 35 USC 112, first paragraph, because the specification, while being enabling for a method for treating hypertrophy in a cardiomyocyte cell, comprising contacting NF-AT3 with an agent that binds to and



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inactivates NF-AT3, wherein said agent is an antibody, does not reasonably provide enablement for a method for treating hypertrophy in a cardiomyocyte cell, comprising contacting NF-AT3 with an agent that binds to and inactivates NF-AT3, wherein said agent is "a small molecule inhibitor". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1, 4, 9 are drawn to a method for treating hypertrophy in a cardiomyocyte cell, comprising contacting NF-AT3 with an agent that binds to and inactivates NF-AT3, wherein said agent is "a small molecule inhibitor".

Claims 1, 4, 9 encompass a method for treating hypertrophy in a cardiomyocyte cell, comprising contacting NF-AT3 with any small molecule that binds to and inactivates NF-AT3, including the contemplated GATA4 mimetics, or an antisense molecule.

The specification proposes a hypothesis that cardiac hypertrophy is caused by activated NF-AT3, which is interacting with GATA4 in cardiomyocyte cells, resulting in up-regulation of cardiac hypertrophic genes, and thus cardiac hypertrophy could be treated if the activity of NF-AT3 is inhibited. The specification discloses the following hypothetical chains of reactions: Hypertrophic stimuli such as AngII and PE, which lead to an elevation of intracellular calcium, result in activation of calcineurin. Calcineurin would dephosphorylate NF-AT3 in the cytoplasm of cardiomyocytes, enabling its translocation to the nucleus, where it can interact with GATA4, resulting in up-regulation of cardiac hypertrophic genes, such as beta-natriuretic peptide (BNP), responsible for

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hypertrophy (p.13, first paragraph and figure 8). The specification discloses that cardiac hypertrophy has been known to be associated with elevation of intracellular calcium (p.9, last paragraph). The specification also discloses that calcineurin, which is a phosphatase, is activated by a sustained calcium plateau, and is insensitive to transient calcium fluxes as occur in response to cardiomyocyte contraction (p.11, last paragraph). The specification further discloses that NF-AT3 is a member of a multigene family comprising NF-ATc, NF-ATp, NF-AT3 and NF-AT4, and that NF-AT3 is expressed in a variety of tissues including the heart. The reference by Hoey et al, 1995 is referred to for the NF-AT3 tissue location information (specification, p.12, second paragraph). In addition, the specification discloses that in T cells, changes in gene expression in response to calcineurin are mediated by members of the NF-AT family of transcriptional factor, which translocate into the nucleus following dephosphorylation by calcineurin (p.13, second paragraph). In example 2 in the specification, from mouse embryo cDNA, numerous GATA4-interacting factors, including NF-AT3, are identified. In example 4, in transfected cardiomyocytes, BNP promoter is activated in the presence of GATA4, NF-AT3 and calcineurin. In example 4, page 75, last paragraph, bridging page 76, antibodies specific for NF-AT3 are able to eliminate complexes formed between BNP promoter and cardiac protein extracts. In example 8, transgenic mice expressing in the hearts mutant NF-AT3, which is constitutively, i.e. continuously, activated, show extensive cardiac hypertrophy.

The specification also discloses that the C-terminal portion of NF-AT3 interacts with the second zinc finger of GATA4 (p.13, third paragraph, p.74, second and third paragraph).

The specification discloses that agent that reduces the expression of NF-AT3 could be an antisense construct or an antibody or a small molecule inhibitor (p.4, last paragraph). The specification contemplates the use of mimetics as small molecule inhibitors that specifically inhibit NF-AT3 protein activity or binding to GATA4, and that said molecule may be sterically similar to the actual target compounds, at least in key portions of the target's structure and or organochemical in structure (p.29, paragraph before last).

It is noted however that there is no disclosure concerning the **configuration** of the second zinc finger of GATA4 or of the C-terminal portion of NF-AT3. There is no disclosure of how to make the claimed GATA4 mimetics, other than a mere disclosure that the claimed mimetics may be "sterically" similar to the actual target compound. Further, there is no disclosure of actual treatment of said hypertrophic transgenic mice with the claimed small molecule inhibitors of NF-AT3, nor treatment of cardiomyocyte cells, which are exposed to hypertrophic stimuli such as AngII and PE, with the claimed small molecule inhibitors.

One could not extrapolate the teaching of the specification to the claims for the following reasons:

Concerning GATA4 mimetics, although one would not doubt that GATA4 does indeed bind to NF-AT3, nor would they challenge the notion that interference with that

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interaction will have inhibitory effects on NF-AT3 ability to activate gene transcription of hypertrophic genes, however without the knowledge of the configuration of the second zinc finger of GATA4, a site for binding of GATA4 to NF-AT3, one would not know how to make the claimed GATA4 mimetics, especially in view of a mere disclosure in the specification that the claimed mimetics may be "sterically" similar to the actual target compound.

In addition, it is unpredictable that the claimed mimetics could be used successfully *in vivo* for treating cardiac hypertrophy. The claimed mimetics must accomplish several tasks to be effective. They must be delivered into the circulation and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. It is clear, as disclosed above that the specification does not teach how to make/use a formulation with a targeting molecule. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The formulation may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the formulation. In addition, the formulation may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the formulation has no effect, circulation into the target area may be insufficient to carry the formulation and a large enough local concentration may not be established.

Concerning using an antisense molecule for the claimed method, the claimed method encompasses gene therapy using antisense. It is well known in the art however gene therapy is unpredictable. As drawn to transgenic mice, in the field of antisense technology, according to Gura (Science, 1995, 270:575-577), researchers have many concerns. Gura discloses that "the biggest concern is that antisense compounds simply don't work the way researchers once thought they did." Other drawbacks in animal studies include difficulty getting antisense oligonucleotides to target tissues and the existence of potentially toxic side effects such as increased blood clotting and cardiovascular problems (page 575, col 1, para 2). Another problem stems from the fact that oligonucleotides used as controls produced the same biological effects in cell culture as did the antisense compounds (page 576, col 1, para 2 and 3). In addition, Gura reports problems with synthetic antisense oligonucleotides in that unwanted and sometimes lethal side effects occurred in animal experiments, and that they block cell migration and adhesion to underlying tissue in vitro (page 576, col 3, para 1 and 3). Thus a high degree of unpredictability is associated with the use of antisense constructs employed in methods of inhibiting expression of a particular protein in an animal model.

Further, the state of the art at the time of filing was that the combination of vector, promoter, protein, cell, target tissue, level of expression and route of administration required to target the tissue of interest and obtain a therapeutic effect using gene therapy was unpredictable. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene

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therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1).

Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

The specification provides insufficient guidance with regard to these issues and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success.

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In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention as broadly as claimed.

#### **REJECTION UNDER 35 USC 102(b)**

Rejection under 35 USC 102(b) of claim 1 pertaining to anticipation by Haverich et al, or Ried et al, as evidenced by McCaffrey et al, and Martinez-Martinez et al remains for reasons already of record in paper No.21.

Applicant asserts that every element of claim 1 is not found in any of the prior art references. None of the recited references teach treatment of hypertrophy or effects on cardiac structure. Haverich et al, Ried et al only teach the use of CsA for treatment of transplantation disease. They are instead directed towards improving cardiac function in a post-transplant environment.

Applicant argues that the references must teach the invention or literally or inherently anticipate the invention. Applicant argues that the Examiner appears to have broadly misapplied the inherency standards, which requires certainty.

Applicant's arguments set forth in paper No.24 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that the claimed method step comprises inhibiting the function of NF-AT3 in a cardiomyocyte, i.e. administering an agent that inhibits the function of NF-AT3 in a cardiomyocyte. It is further noted that as written, the claimed target composition is a cardiomyocyte.

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It is noted that Applicant did not address the issue raised by the teaching of Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Contrary to Applicant assertions, it is clear that the claimed invention is inherently anticipated by the prior art, based on the teaching of Ex parte Novitski 26 USPQ 1389 (BPAI 1993), i.e, the method of the prior art comprises the same method step as claimed in the instant invention using the same composition.

Haverich et al recite the study of Gao et al, in which Cyclosporin A is administered in patients after heart transplantation ( p.2714, and table 1). Reid et al teach administration of Cyclosporin A to patients one year after heart transplantation (p.399, first column, paragraph under immunosuppression). . It is noted that Cyclosporin A administered to patients after cardiac transplantation, as taught by Haverich et al, or Ried et al would inherently inhibit NFAT3, because such inhibition is the property of cyclosporin A, as evidenced by Martinez-Martinez et al.

Thus the method taught by Haverich et al, or Ried et al has the same method step, using the same composition as the claimed method.

Although the references do not recite treatment of hypertrophy, however, because the method of the prior art comprises the same method step as claimed in the instant invention using the same composition, i.e. a compound that inhibits the function of NF-AT3, and the same target composition, i.e. cardiomyocytes, the claimed method is anticipated because the method will inherently lead to the claimed effects. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).



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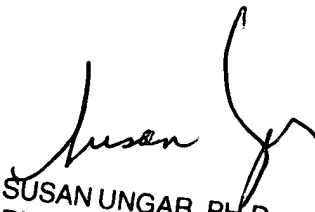
Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

July 7, 2003

  
SUSAN UNGAR, PH.D  
PRIMARY EXAMINER

  
ANTHONY C. CAPUTA  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600